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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,534	11/21/2003	Anthony H. Cincotta	02591/100B206-US3	3460

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,534	CINCOTTA ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/26/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 6/27/07 in response to the Office Action of 12/27/06 are acknowledged and have been entered.

Claims 23-24 have been added by Applicant.

Claims 1-19 and 21-24 are pending and are currently under examination.

Response to Arguments

Double Patenting Rejection and 35 U.S.C. 103(a) Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6, 10, 15, 21, and 22 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 8, 13, and 19 of U.S. Patent No. 5,792,748 in view of Werning et al (Arch. Ontolaryngol. Head Neck Surg., 7/95, 121:783-789) and Cincotta et al (Cancer Research, 1994, 54:1249-1258) as evidenced by Molitch (Endocrinol. Metab. Clin. North Am., 1992, 21(4) abstract) for the reasons stated in the Office Action of 12/27/06 and for the reasons set-forth below.

Further, claims 1-19 and 21-22 remain rejected and newly added claims 23-24 are rejected under 35 U.S.C. 103(a) as being obvious over Cincotta et al (US Patent 5,792,748; filed 6/7/95) in view of Werning et al (Arch. Ontolaryngol. Head Neck Surg., 7/95, 121:783-789) and Cincotta et al (Cancer Research, 1994, 54:1249-1258), as evidenced by Molitch (Endocrinol. Metab. Clin. North Am., 1992, 21(4):abstract), for the reasons stated in the Office Action of 12/27/06 and for the reasons set-forth below.

It is noted that newly added claim 23 recites: "The method of claim 1, wherein said step of adjusting the daily plasma prolactin profile of said tumor bearing mammal comprises administering said prolactin enhancer within the peak prolactin period of said healthy mammal of the same species and sex as said tumor bearing animal". Further, newly added claim 24 recites: "The method of claim 1, wherein said prolactin enhancer is administered between the hours of 01:00 and 04:00".

The Office Action of 12/27/06 contains the following text:

"Claim 3 of US Patent No. 5,792,748 is drawn to a method for inhibiting neoplastic growth in a mammal in need of such treatment comprising administering

prolactin at a predetermined time during a 24-hr period. Claim 8 of US Patent No. 5,792,748 is drawn to the method of claim 3, wherein said administration adjusts the prolactin profile of said mammal to conform to or approach the standard profile of a healthy mammal of the same species and sex. Claim 13 of US Patent No. 5,792,748 is drawn to the method of claim 8 wherein the mammal is a human. Claim 19 of US Patent No. 5,792,748 is drawn to the method of claim 13, wherein said neoplasm is a member selected from the group consisting of sarcomas, fibrosarcoms, carcinomas, glioblastomas, and melanomas.

Werning et al teaches that combining photodynamic therapy (exposing said contacted tumor cells to light) with metoclopramide increases the percentage of tumor regression versus photodynamic therapy alone (see abstract). Metoclopramide, as evidenced by Molitch, is a prolactin enhancer.

Cincotta et al teaches that 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride is a photodynamic agent which activates solid tumors (page 1257, in particular) and that photodynamic therapy with 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride in mice resulted in direct tumor cell killing (see abstract, in particular).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to optimize the claimed invention of Cincatta et al (US Patent 5,792,748) so as to include photodynamic therapy. One would have been motivated to do so because it was previously taught in the art that combining photodynamic therapy with the administration of a prolactin enhancer resulted in the

increased regression of tumors versus prolactin enhancer therapy alone. Furthermore, the teachings of Cincatta et al (Cancer Research, 1994) promote the use of highly selective photosensitizers, like 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride, for optimizing cell killing with photodynamic therapy. Thus, clearly, the combined teachings suggest to one of skill in the art a reasonable expectation of success in arresting the growth of or eradicating tumors by combining photodynamic therapy with the administration of prolactin enhancers."

It is further noted that Cincotta et al (US Patent 5,792,748) further teaches administering said prolactin enhancer within the peak prolactin period of said healthy mammal of the same species and sex as said tumor bearing animal wherein said prolactin enhancer is administered between the hours of 01:00 and 04:00 (see lines 50 of column 5 to line 6 of column 6 of Cincotta et al (US Patent 5,792,748), in particular).

In the Reply of 6/27/07, Applicant argues that the effect observed in Werning is unrelated to metoclopramide's action on prolactin and is unrelated to resetting the prolactin rhythm of a tumor bearing mammal. Applicant states that the discussion in Werning is restricted to metoclopramide and effects attributable to metoclopramide. Applicant states there is no disclosure in Werning that the effect obtained by combining metoclopramide administration and photodynamic therapy (PDT) is related to plasma prolactin levels. Applicant further states that prolactin is not mentioned in Werning and that Werning does not suggest that the effects of metoclopramide in combination with PDT are mediated through plasma prolactin levels. Applicant further states that Molitch's disclosure that metoclopramide is a prolactin enhancer does not provide

motivation to combine Cincotta with Werning and states that Werning teaches that the prolactin enhancing activity of metoclopramide is not related to the observed enhancement of PDT. Applicant further states that Werning teaches that doses of 16, 32 and 48 mg/kg, respectively, show greatest efficacy in treating tumors when combined with PDT. Applicant interprets the teachings of Werning to suggest that Werning teaches that the metoclopramide dose should be maximized to effect treatments with PDT. Applicant further states that adjusting the plasma prolactin profile of a tumor bearing mammal to approach the profile of a normal mammal requires that the prolactin enhancer not be administered to maximize prolactin levels, but would instead lead to uniformly high levels of plasma prolactin. Applicant states this is in direct conflict with the teaching of the '748 patent and the instant claims. Applicant further cites Molitch: "Pathologic increases of PRL [prolactin] owing to hypothalamic dysregulation occur with a variety of medications, including...metoclopramide." Applicant argues that Molitch does not evidence that metoclopramide, as administered in Werning, is a prolactin enhancer that may be used in combination with the '748 patent to arrive at the instant claims. Applicant further states that Molitch teaches explicitly that metoclopramide cannot be used to reset the daily plasma prolactin profile of a tumor bearing mammal to approach the profile of a normal mammal. Applicant further argues that unexpected results were obtained with the combination of prolactin resetting therapy and PDT compared to either therapy alone. Applicant states that Examples 1-2, and Figure 5 demonstrate synergistic effects when PDT is combined with

NRT using a prolactin enhancer. Applicant further states that there is no suggestion in the prior art that synergistic effects could be achieved.

The arguments found in the Reply of 6/27/07 have been carefully considered, but are not deemed persuasive. In regards to the argument that the effect observed in Werning is unrelated to metoclopramide's action on prolactin and is unrelated to resetting the prolactin rhythm of a tumor bearing mammal, Werning does not teach that the effect observed in Werning is unrelated to Metoclopramide's action on prolactin or is unrelated to resetting the prolactin rhythm of a tumor bearing mammal. Said argument is mere speculation.

In regards to the argument that there is no disclosure in Werning that the effect obtained by combining metoclopramide administration and photodynamic therapy (PDT) is related to plasma prolactin levels, said effect is made evident in view of the teaching of Molitch that metoclopramide is a prolactin enhancer.

In regards to the argument that that Molitch's disclosure that metoclopramide is a prolactin enhancer does not provide motivation to combine Cincotta with Werning, the Examiner respectfully disagrees. Cincotta claims a method of treating tumors by administering a prolactin enhancer. Werning, in view of Molitch, teaches metoclopramide is a prolactin enhancer that treats tumors in combination with PDT. Thus, it would have been obvious to combine Cincotta with Werning to treat tumors.

In regards to the argument that Werning teaches that the prolactin enhancing activity of metoclopramide is not related to the observed enhancement of PDT, there is no teaching in Werning that the prolactin enhancing activity of metoclopramide is not

related to the observed enhancement of PDT. Said argument is mere speculation and Applicant's statement that "Prolactin is not mentioned even once in Werning" further supports that Werning does not teach that prolactin enhancing activity of metoclopramide is not related to the observed enhancement of PDT (see page 8 of the Reply of 6/27/07).

In regards to the argument that adjusting the plasma prolactin profile of a tumor bearing mammal to approach the profile of a normal mammal requires that the prolactin enhancer not be administered to maximize prolactin levels (which Applicant interprets from the data taught by Werning), but would instead lead to uniformly high levels of plasma prolactin, a method of "maximizing" prolactin levels is neither implied nor demonstrated by Werning. Werning does not explicitly or implicitly teach that prolactin levels should be "maximized". Rather, Werning teaches a range in which a prolactin enhancer can be administered in conjunction with PDT to ablate tumors and prevent regrowth of tumors.

In regards to the argument that Molitch does not evidence that metoclopramide, as administered in Werning, is a prolactin enhancer that may be used in combination with the '748 patent to arrive at the instant claims, Molitch is merely cited to identify that metoclopramide was known in the art as a species of prolactin enhancers.

In regards to the argument that Molitch teaches explicitly that metoclopramide cannot be used to reset the daily plasma prolactin profile of a tumor bearing mammal to approach the profile of a normal mammal, there is no such teaching in Molitch that

metoclopramide cannot be used to reset the daily plasma prolactin profile of a tumor bearing mammal to approach the profile of a normal mammal.

In regards to the argument that unexpected results were obtained with the combination of prolactin resetting therapy and PDT compared to either therapy alone, this argument has been considered but is not found persuasive in view of the teachings of Werning. It is noted that unexpected results, such as a demonstration of synergy, are used to overcome obviousness rejections for combining methods taught by separate references (see MPEP 716.02(a)). However, in the instant case, methods of combining PDT with metoclopramide (a prolactin enhancer) are anticipated by a *single reference*. Further, Werning teaches, *in a single reference*, the result that combing PDT with metoclopramide (a prolactin enhancer) results in 100% tumor regression without re-growth. Therefore, the prior art has already demonstrated, in a single reference, that combing PDT with metoclopramide (a prolactin enhancer) results in 100% tumor regression without re-growth. Thus, Applicant's arguments have not been found persuasive and the rejections are maintained.

Double Patenting Rejection

Claims 1-4, 10, 15, and 21 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 13, 28, and 30 of U.S. Patent No. 6,071,914 in view of Lin (Cancer Cells, 1991, 3(11)) and Cincotta et al (Cancer Research, 1994, 54:1249-1258) for the reasons stated in the Office Action of 12/27/06 and for the reasons set-forth below.

The Office Action of 12/27/06 contains the following text:

"Claim 1 of U.S. Patent 6,071,914 is drawn to a method for treating a patient suffering from a neoplasm comprising the steps of: comparing the blood prolactin level of said patient at each of a plurality of spaced apart time points during a 24-hour period to the corresponding prolactin level of a baseline prolactin level of healthy humans of the same sex as said patient; and adjusting the prolactin level of said patient to cause the patient's prolactin profile approach or conform to the baseline prolactin profile by administering a prolactin reducer to said mammal at a predetermined time, thereby inhibiting growth of said neoplasm in said human. Claim 12 of U.S. Patent 6,071,914 is drawn to the method of claim 1, further comprising administering a prolactin enhancer to said patient. Claim 13 of U.S. Patent 6,071,914 is drawn to the method of claim 12, wherein said prolactin reducer is bromocriptine and said prolactin enhancer is melatonin. Claim 18 of U.S. Patent 6,071,914 is drawn to a method for treating a patient suffering from a neoplasm comprising adjusting the prolactin level of said patient to cause the patient's prolactin profile to approach or conform to the baseline prolactin profile by administering a prolactin reducer to said patient at a predetermined time, thereby inhibiting the growth of said neoplasm in said human. Claim 28 of U.S. Patent 6,071,914 is drawn to the method of claim 18, wherein said method further comprises administering a prolactin enhancer to said patient. Claim 30 of U.S. Patent 6,071,914 is drawn to the method of claim 28, wherein said prolactin reducer is bromocriptine and said prolactin enhancer is melatonin.

Lin summarizes the state of the art of photodynamic therapy of malignant tumors, including the use of selective photosensitizers like phthalocyanine dyes and iodinated benzophenothiazine (pages 439-439, in particular).

Cincotta et al (Cancer Research) also teaches that photodynamic therapy is a promising new approach for the selective eradication of neoplastic tissue and further teaches the successful use of 5-ethylamino-9-diethylamino-benzo[a]phenothiazinium chloride. A benzophenoxazine analog, as a photosensitizing agent and teaches a method of treating tumors in a mammal with said photosensitizing agent and that photodynamic therapy of EMT-6 tumors in mice with said photosensitizing agent resulted in direct tumor cell killing.

In the absence of unexpected results, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine photodynamic therapy with the patented invention of adjusting prolactin levels since each of these methods had been taught by the prior art to successfully eradicate neoplasm. Clearly, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Thus, one of ordinary skill in the art would have reasonably expected to successfully treat tumors using both methods combined."

In the Reply of 6/27/07, Applicant states: "For the reasons identical to those set forth above in Section IV the claims are not obvious over the combination of the teachings of the '914 patent and Cincotta, because unexpected results are obtained with the combination of NRT and PDT, compared to either therapy alone".

The arguments found in the Reply of 6/27/07 have been carefully considered, but are not deemed persuasive. These arguments have been addressed above. Thus, Applicant's arguments have not been found persuasive and the rejection is maintained.

Summary

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a). A shortened statutory period for response to this Final Action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this Final Action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. '1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than six months from the date of this Final Action.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

/Misook Yu/
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